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P2419 OXA-48 beta-lactamase inhibitors with reversible and competitive mechanisms of action

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Background: Even now, some 70 years after their introduction, β-lactam antibiotics still represent the most generally used anti-infective drugs. Serious bacterial resistance to β-lactams has arisen, of course, particularly through the evolution of β-lactamases. A prevalent serine β-lactamase which has already caused outbreaks of antibiotic resistant bacteria all over the world is OXA-48, an oxacillinase belonging to the carbapenem-hydrolyzing class D β-lactamases. The newest effort to circumvent resistance is the development of novel chemical class of β-lactamase inhibitors.

Materials/methods: The compounds were tested using fluorescence quenching nitrocefin enzymatic assay. The mechanism of action of the hits was evaluated performing time dependence of enzyme inhibition test to assign reversible or non-reversible inhibition. The characterization of the reversible inhibitors was performed by the determination of the apparent Km and Vmax of nitrocefin in the presence of the selected inhibitors.

Results: At the beginning of the program we have screened a proper compound collection consisting of 35.000 compounds. High-throughput screening resulted in 436 OXA-48 β-lactamase inhibitors with IC_{50} values in the micromolar range, divided into 22 chemical classes according to their central core and functional moieties. The most promising inhibitors have been characterized in terms of mechanism of action resulting in a reversible and competitive inhibition. Moreover, the most relevant chemical scaffolds were explored using the structure-based design. Focused libraries were synthetized to define structure−activity relationships and to develop the hit compounds into more potent inhibitors reaching best optimized IC_{50} values of 30 nanomolar.

Conclusions: The hit optimization activity led to the identification of new reversible and competitive OXA-48 inhibitors in nanomolar range. The program, currently in the hit to lead stage, includes computer-driven drug design of interesting compounds by iteratively exploring the most promising chemical classes for the identification of more potent inhibitors of the OXA-48 β-lactamase.